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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/611,598	06/30/2003	Johannes B.M.M. Van Bree	16994G-012730US	2502

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EXAMINER	
PRATS, FRANCISCO CHANDLER	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 11/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/611,598	VAN BREE ET AL.	
	Examiner	Art Unit	
	Francisco C. Prats	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 35-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 35-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11-24-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The preliminary amendment filed June 30, 2003, has been received and entered.

Claims 1 and 35-64 are pending and are examined on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35-64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, the specification as filed fails to demonstrate that administration of the enzyme, using any of the disclosed or claimed regimens, results in a measurable clinical therapeutic effect which alleviates symptoms of infantile Pompe disease, such that the patient will predictably survive past one

year of age. It is noted that the specification at pages 37-39 describes protocols for clinical trials for infant patients, and that page 42 of the specification provides an infusion schedule for infant patients. However, none of this disclosure appears to present any significant data because no clear results are presented. Moreover, although applicant presents data using a mouse model (specification, pages 27-35), it is not clear what that model is, such that an independent assessment of the presented results can be made and correlated with the expectation of infantile Pompe disease treatment.

Conversely, each of de Barsy et al (Birth Defects, Original Article Series, Vol. IX, No.2, pages 184-190 (1973)) and Williams et al (Birth Defects: Original Article Series, Vol. XVI, No. 1, pages 415-423 (1980)) discloses that, although one can measure a therapeutic effect manifested as an increase in enzyme activity in the tissues of infant patients after administration of the enzyme (e.g., de Barsy at page 186, left column; Williams at page 420, second paragraph), the treatment regimens disclosed therein failed to alleviate the outward symptoms of the disease, with de Barsy's treatment regimen resulting in death at less than one year of age. Thus, the lack of success of treating clinical symptoms of Pompe disease demonstrated by de Barsy and Williams, combined with the lack of

disclosure in the as-filed specification for a treatment regimen which actually produces a clinical result with respect to alleviating symptoms, clearly demonstrates that the skilled artisan would have been required to have conducted significant experimentation to ascertain which if any of the disclosed treatment regimens would have resulted in a reduction in symptoms of Pompe disease such that patients would predictably survive to an age greater than one year old, as presently recited in the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claim 1 is rejected under 35 U.S.C. 102(a) as being anticipated by Kikuchi et al (J. Clin. Invest. 101(4):827-833 (1998)).

Kikuchi discloses the treatment of Pompe's disease in quail by administering to the quail patients, every 2-3 days for 18 days, by intravenous injection, 14 mg/kg body weight of recombinant human acid α-glucosidase in precursor form having 90% of the enzyme in the 110 kD form. Kikuchi also discloses the therapeutic efficacy of the treatment by disclosing that the administration results in normal histopathology in the heart and liver. Note that Kikuchi's enzyme would be indistinguishable from that produced in the milk of a transgenic animal. A holding of anticipation over the cited claims is therefore clearly required.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by de Barsy et al (Birth Defects, Original Article Series, Vol. IX, No.2, pages 184-190 (1973)) or Williams et al (Birth Defects: Original Article Series, Vol. XVI, No. 1, pages 415-423 (1980)).

The de Barsy reference discloses the treatment of Pompe's disease in a human infant patient by administering, in a single intravenous injection, 22 units of human acid α-glucosidase from

placenta. Using the value of 7300 Units per mg protein on page 185, this means that about 3 mg of enzyme were administered to the patient. Assuming the infant weighed at least several kilograms, the administration rate was likely somewhere about 1 mg/kg. While the reference explicitly states that the treatment resulted in no conspicuous morphologic or clinical improvements, it is noted specifically that liver enzyme concentration was improved over baseline from 32 to 142 hours after enzyme administration and that muscle enzyme concentration was improved at 149 hours after administration. Thus, the treatment in the reference can be considered as having had a therapeutic effect.

Similarly, although Williams' administration of 3 mg of enzyme, followed by an administration of 13 mg of enzyme, does not result in changes in the clinical symptomology of the disease, Williams clearly discloses a therapeutic effect by disclosing a measurable increase in enzyme activity in tissues (page 420, second paragraph) after enzyme administration. Thus, a holding of anticipation over the cited claims is therefore required.

Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by Reuser et al (U.S. Pat. 6,118,045).

Reuser discloses and claims a composition for the treatment

of Pompe's disease in a human patient by intravenous injection, said composition comprising human acid α-glucosidase, obtainable from the milk of a transgenic animal. *See, e.g.,* claims 18-20 at col. 18. A holding of anticipation over the cited claims is therefore required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35

U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 35-64 are rejected under 35 U.S.C. 103(a) as being unpatentable de Barsy et al (Birth Defects, Original Article Series, Vol. IX, No.2, pages 184-190 (1973)), Williams et al (Birth Defects: Original Article Series, Vol. XVI, No. 1, pages 415-423 (1980)) and Reuser et al (U.S. Pat. 6,118,045), in view of Bijvoet et al (Biochim. Biophys. Acta 1308:93-96 (1996)) and Van Hove et al (Biochem. Mol. Biol Int'l. 43(3):613-623 (1997)).

The claims recite the treatment of infantile Pompe's disease wherein at least 10 mg/kg body weight per week of human acid α-glucosidase are administered to a patient which survives at least to one year of age. Each of de Barsy, Williams and Reuser suggest the treatment of infantile Pompe's disease by administering human acid α-glucosidase to patients in need thereof. Note specifically that, although the symptoms of the disease were not alleviated in the treatment regimens of de Barsy and Williams, each of those references demonstrates a therapeutic effect, demonstrated as an increase in enzyme activity in the tissues of infant patients after administration of the enzyme (e.g., de Barsy at page 186, left column; Williams at page 420, second paragraph). Note further Reuser's disclosure of the uptake of active enzymes in fibroblasts from

Pompe patients (column 16, lines 37-65). Note still further that Williams' patient was 13 months old at the start of the treatment regimen (page 418), thereby providing an expectation that the claimed treatment regimes, which use greater enzyme amounts, would have resulted in a patient survival of over one year of age.

DeBarsy, Williams and Reuser differ from the claims in that the dosage amounts disclosed therein are smaller than those recited in various embodiments recited in applicant's claims, and that the dosages are not gradually increased as recited in some other embodiments in the claims.

However, de Barsy notes that the lack of significant clinical effects was likely due to the small amount of enzyme administered owing to lack of availability, and that the efforts disclosed therein must be considered preliminary. *See* p. 189, col. 1. Thus, de Barsy clearly suggests that increased dosage would be desirable in treating the disease. Moreover, each of Reuser (claims 18-20), Bijvoet (abstract at page 94, disclosing *in vitro* internalization of enzyme) and Van Hove (sentence spanning pages 613 and 614, disclosing endocytosis of 110 kD form of the enzyme and delivery to liver and heart upon injection) clearly suggest that relatively large amounts of the enzyme are obtained by the methods disclosed therein, and that

the enzymes prepared therein are suitably targeted to the desired tissues, including muscle.

Thus, the artisan of ordinary skill, recognizing from de Barsy that high dosages would have been reasonably expected to improve the results disclosed therein, would have been motivated to have increased the enzyme dosage to the amounts recited in applicant's claims, suitable quantities of the enzymes being made available by the techniques disclosed in the Reuser, Bijvoet and Van Hove disclosures.

Moreover, the determination of a suitable dosage regimen, including the gradually increasing dosage regimen recited in the claims, clearly would have been a matter of routine optimization on the part of the artisan of ordinary skill, the determination of suitable treatment regimens being routinely determined in the pharmaceutical arts. Thus, absent some demonstration of an unexpected result, the claims must be considered obvious. In this regard note that the clinical trials described in the specification at pages 37-39 do not appear to present any significant data in that no clear results are presented. Therefore, it is respectfully submitted that no unexpected result has been demonstrated on the record.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Francisco C. Prats whose telephone number is 571-272-0921. The examiner can normally be reached on Monday through Friday, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Francisco C. Prats
Primary Examiner
Art Unit 1651

FCP